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SOME HIGHLIGHTS IN THE STRUCTURAL AND SYNTHETIC CHEMISTRY OF THE ACONITE ALKALOIDS

A PERSONAL HISTORICAL PERSPECTIVE†

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INTRODUCTION

My work on diterpene alkaloids lasted more than 30 years and it has been said to have culminated with the synthesis of hexacyclic polysubstituted derivatives of the delphinine type. However, this is not my opinion. Structural studies on highly complex natural products of unprecedented type during the classical pre-NMR era seemed as exciting to me as synthesis and, in fact, it is the structural work that I remember with the greatest pleasure. While it is clearly impossible to review 30 years of chemistry in one article, I shall discuss certain selected high points which to me are specially fascinating and might interest even today's readers.

I started thinking about the structure of the complex aconitum and delphinium alkaloids in the forties when I was working with Professor Vladimir Prelog in Zürich. I was naturally influenced by the triterpene work‡ going on all around me at the famous E.T.H. laboratory and thus my first idea, how to clear up the hopeless confusion in the chemistry of aconitine and delphinine, was to use Professor Ruzicka's method of dehydrogenation on these compounds. However, further reading of the literature disclosed that this had been tried without success many times. Thus, I was forced to conclude that the best way to approach the problem would be to solve first the structure of some much simpler member of the same class.

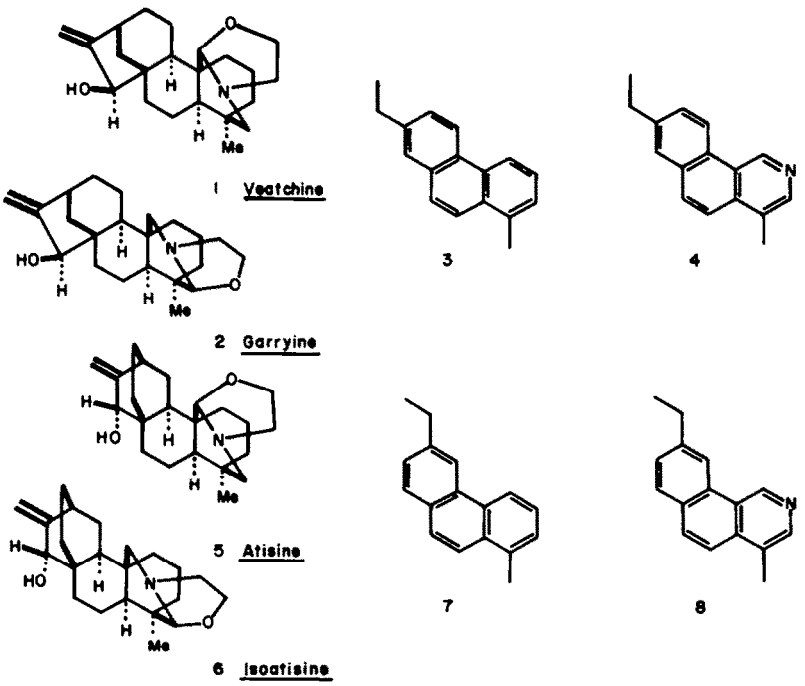
When I moved in 1948 to the University of New Brunswick, I decided that the simple aconite alkaloid atisine would be a suitable target. Since I found myself unable to obtain a large supply of atisine, I settled finally on the alkaloids of *Garrya veatchii*. Nothing was known about these compounds except that they were isomeric with atisine. The fortunate decision to work on the Garrya alkaloids and the rapid solution of their structure are the original reasons of my staying with the problem of the aconitum alkaloids for such a long time and my writing this article now.

THE STRUCTURES OF THE FIRST C_{20} DITERPENE ALKALOIDS

As shown in Scheme 1, the Garrya alkaloids yielded 1-methyl-7-ethylphenanthrene (**3**) and 1-methyl-7-ethyl-3-azaphenanthrene (**4**) on selenium dehydrogenation and this was a give-away of their

† 1983 Guenther Award Lecture.

‡ In my time much of this work was under the dynamic supervision of Oskar Jeger and it is a source of great satisfaction for me that he preceded me as a recipient of the Guenther Award.



Scheme 1.

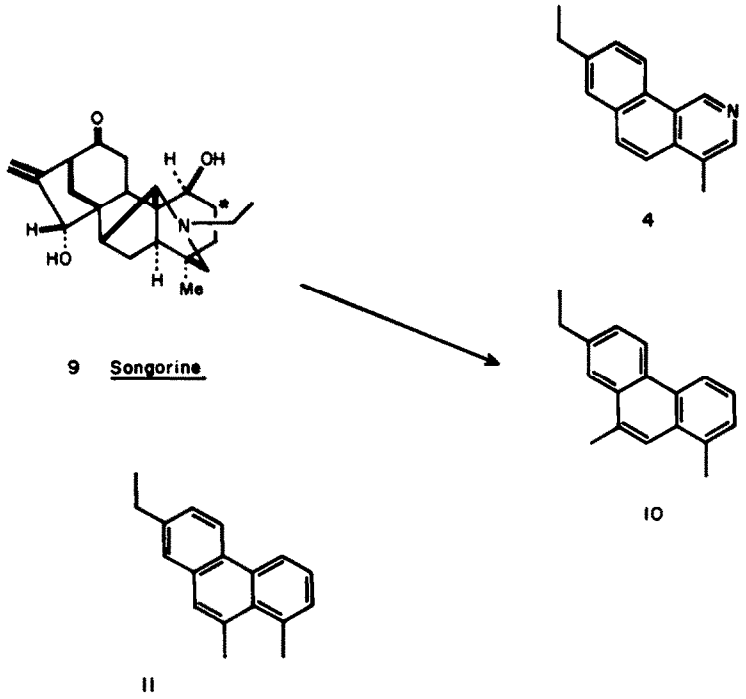
skeletal structure. It was relatively easy to fit in the functional groups and we proposed the flat structures (**1** and **2**) late in 1953[1] and the stereochemistry less than two years later.[2]

Many chemical transformations of the alkaloid atisine were known thanks to the meticulous researches in W. A. Jacob's laboratory at the Rockefeller Institute. I had noticed that there was an extensive parallelism between the transformations of atisine and the Garrya alkaloids. Moreover, atisine gave, on dehydrogenation, 1-methyl-6-ethylphenanthrene (**7**) and a base very similar to our azaphenanthrene which I presumed to be 1-methyl-6-ethyl-3-azaphenanthrene (**8**). Consequently, I suggested for the atisine skeleton in the same paper[1] the analogous flat formula (**5**) which differed from our Garrya structures by having a [2.2.2]- instead of a [3.2.1]-bicyclooctane system. The stereochemistry of atisine was later elucidated in a series of elegant studies by S. W. Pelletier and by D. Dvornik and O. E. Edwards.

The pentacyclic Garrya alkaloids and atisine gave us the first idea of the skeletal type of the aconitum alkaloids. However, before attacking the Mount Everest of aconitine and delphinine, I wished to get some intermediate experience, preferably with a hexacyclic representative of the class which would not have too many substituents and would yield dehydrogenation products with selenium. Again, luck played an important role. I selected the minor alkaloids napelline and the corresponding ketone songorine isolated from the mother liquors of aconitine for study. They turned out to be ideally suited for our purpose.

In the structure determination of songorine, I received an unexpected assist from Dr. A. Kuzovkov from the Institute of Plant Chemistry, Moscow. In our hands selenium dehydrogenation of napelline gave the same azaphenanthrene (**4**) as the Garrya alkaloids and a mixture of phenanthrenes which we were unable to resolve and identify. This seemed to nail down the Garrya skeletal type, but gave no indication as to the location of the additional ring. At this point, A. Kuzovkov informed me that under somewhat different conditions dehydrogenation of songorine yielded a dimethylethylphenanthrene which was identified by synthesis as 1,10-dimethyl-7-ethylphenanthrene (**11**). Since, however, Kuzovkov's last synthetic step was a dehydrogenation I suggested that a methyl migration might have occurred and that the product in question was actually 1,9-dimethyl-7-ethylphenanthrene (**10**). This suggestion was rapidly confirmed by Kuzovkov himself and several other groups.

Thus the skeletal structure (**9**) shown in the scheme was simply arrived at and the functionality fitted in by simple transformations and a consideration of the UV spectrum of songorine (λ_{max} = 290 nm, log ε = 2.6) which indicated overlap of the π orbitals of the exocyclic methylene group and the ketone. Not



Scheme 2.

having enough substance for a more detailed study, I made the mistake of locating originally the ring A hydroxyl at the position marked by the asterisk.[3] This error was rapidly corrected by a Japanese group and thus the formula (**9**) was practically assured. We have proved it rigorously by two total syntheses.[4a,b]

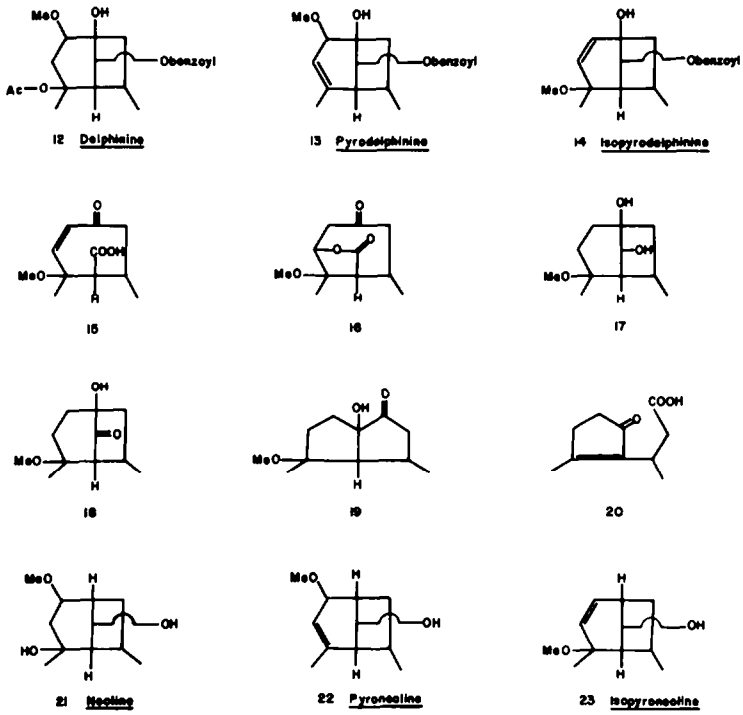
We have seen that L. Ruzicka's dehydrogenation method has given us a clear idea of the structural type of the aconite alkaloids and specifically of the manner in which the nitrogen is built into the diterpenoid system. As I had expected, this information had to be gleaned from the study of not too heavily functionalized members of the class.

THE STRUCTURES OF DELPHININE AND ACONITINE

Simultaneously with this work, the chemistry of delphinine and aconitine was studied systematically in my laboratory. In these studies the precise experimental work of W. A. Jacobs and his collaborators, most importantly S. W. Pelletier, at the Rockefeller Institute was of great value. Careful repetition and analysis of this work supplemented by our own additional experiments enabled us first to deduce the partial structures shown in Scheme 3 for delphinine (**12**), its pyrolysis product pyrodelphinine (**13**) and isopyrodelphinine (**14**) obtained from the last compound by reflux in acidic methanol. The derivation of these partial structures was of key importance in the cracking of the delphinine puzzle and it was achieved essentially by oxidative methods with extensive use of infrared spectrometry, but naturally no proton magnetic resonance or mass spectrometry. As in many other instances, we have found it advantageous not to work with the alkaloids themselves, but with the corresponding neutral amides. In this case our starting material was α-oxodelphinine, which had been already shown by Pelletier and Jacobs to be an N-formyl derivative. Since the degradation of **12**, **13** and **14** was very similar, we shall deal only with the isopyrodelphinine system (**14**), which we solved first.

Hydrolysis of the benzoyl group in α-oxoisopyrodelphinine represented by the partial formula **14** gave the corresponding diol which was oxidized to the α,β-unsaturated keto acid (**15**). The acid **15** showed a UV maximum at 235 nm (log $\varepsilon = 3.8$) and was easily isomerized into the γ-lactone (**16**). Compound **16** displayed two maxima in the carbonyl region of the IR spectrum: 1706 cm^{-1} (ketone) and 1783 cm^{-1} (γ-lactone).

Hydrogenation of **14** followed by alkaline hydrolysis yielded dihydro-α-oxoisopyrodelphonine (**17**) and this compound was oxidized to the corresponding ketone, dihydro-α-oxoisopyrodelphonone (**18**).

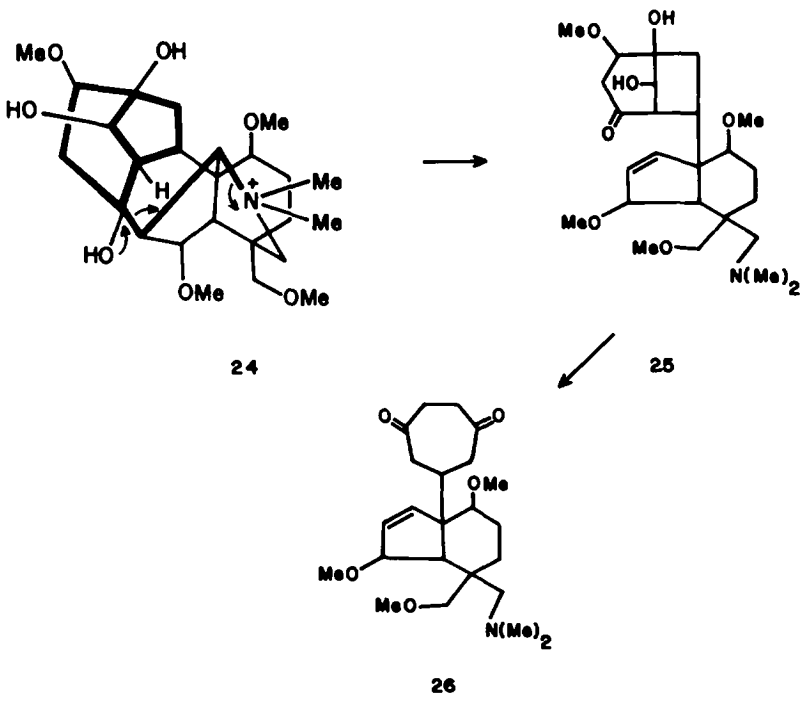


Scheme 3.

Compound **18** showed a peak at 1754 cm^{-1} in the carbonyl region of the IR spectrum in agreement with its formulation as a 5-membered ring ketone. Treatment of **18** with alkali caused an isomerization to a more levorotatory isomer ($\Delta_{\alpha_D} \sim -110°$) which presumably also had a ketone in a 5-membered ring (1747 cm^{-1}). Since there was no way to formulate this isomerization as an epimerization of a chiral centre adjacent to the carbonyl group, we assigned to the product the partial formula **19** and regarded the reaction as an acyloin rearrangement. The α-ketol (**19**) took up 1 mol of periodic acid and yielded after elimination of the methoxy group, the α,β-unsaturated keto acid (**20**). Compound **20** had a UV spectrum ($\lambda_{max} = 250$ nm, log $\varepsilon = 4$) which troubled me for a short time, since it was shifted by approximately 10–15 nm to higher wavelength with respect to our expectations based on spectra of many known cyclopentenones. However, I soon found data in the literature which indicated that cyclopentenones are susceptible to spectral anomalies due to strain.

It can be clearly seen that the transformations discussed above define the entire [3.2.1]-bicyclooctane system and the location of all substituents in the partial structure **14**. The partial formulae **13** and **12** for α-oxopyrodelphinine and α-oxodelphinine, respectively, were deduced in an exactly similar way and it thus became apparent that the pyro-isopyro isomerization must be an allylic rearrangement. The courtesy of Dr. R. S. Stuart at the Merck Laboratories in Montreal enabled us to confirm by radioactive labeling that the methoxyl in **14** is derived from the solvent and that it is this same methoxyl which is eliminated in the formation of the keto acid (**20**). At first we did not know if and how our partial formula fitted into the Garrya-aconite skeleton. It was again a simpler representative of the same class that gave the first clue. We studied another minor component of the aconitine mother liquors simultaneously with delphinine. It was the slightly simpler alkaloid neoline and we showed that it contained the partial structure **21** analogous to delphinine and gave quite analogous reactions (**22**, **23**).

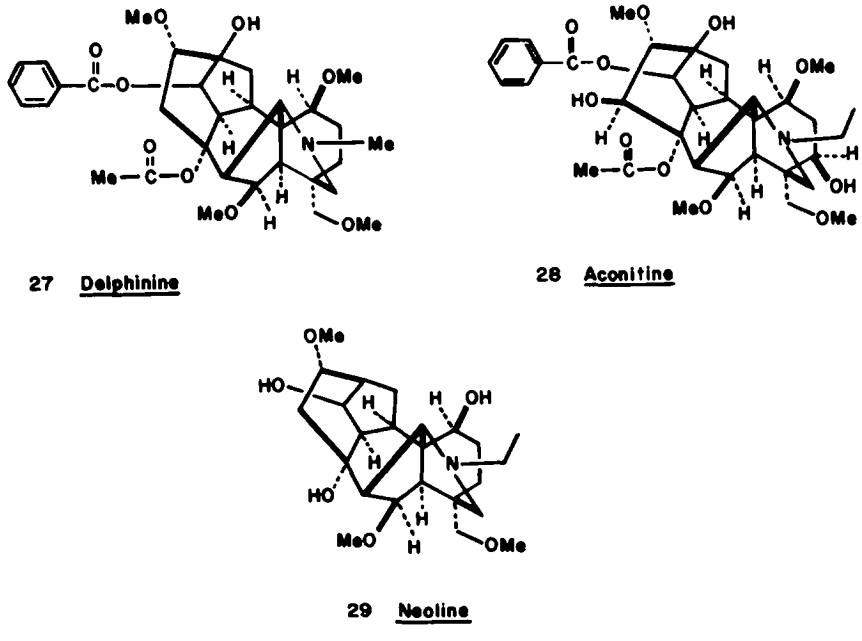
Now the important thing was that neoline also gave recognizable dehydrogenation products. We obtained a good yield of 1-methyl-3-azaphenanthrene and of an unidentified dimethylethyl-phenanthrene. This indicated clearly that the skeletal type of the product being dehydrogenated must be the same as in the alkaloids studied previously. Since the rigorously established partial structure did not fit into this skeletal type, the dehydrogenation must have been preceded by a rearrangement. I shall not elaborate the lengthy, rigorous argument which involved the consideration of several possibilities but show instead in Scheme 4 the outcome of the Hofmann degradation of delphonine methohydroxide



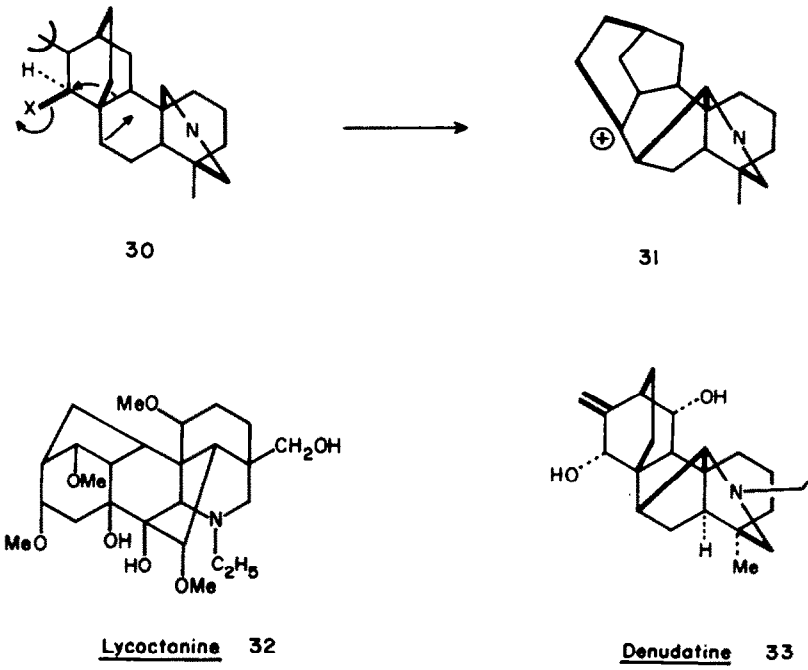
Scheme 4.

(**24**). This remarkable transformation enabled us to relate the [3.2.1]-bicyclooctane partial structure to the nitrogen and thus to orientate it in our well-known diterpene alkaloid skeleton.

We see that the rigorously established known area of delphonine (drawn in heavy lines in formula **24**) was the one which contained all the novel features. It did not take too much imagination to complete the structure in a manner analogous to the Garrya alkaloids and atisine. Also the location of the remaining substituents was relatively facile and I shall not discuss it in this article.



Scheme 5.



Lycoctonine 32 Denudatine 33

Scheme 6.

Thus we deduced the flat structure of delphinine[5] (**27**) and aconitine[6] (**28**), the latter in collaboration with Professor George Büchi in 1959.†

The configuration of these compounds was arrived at very shortly and I shall not deal with it in detail. We deduced the structure of neoline[7] (**29**) including the configuration in 1960 and corroborated it by total synthesis 17 years later.

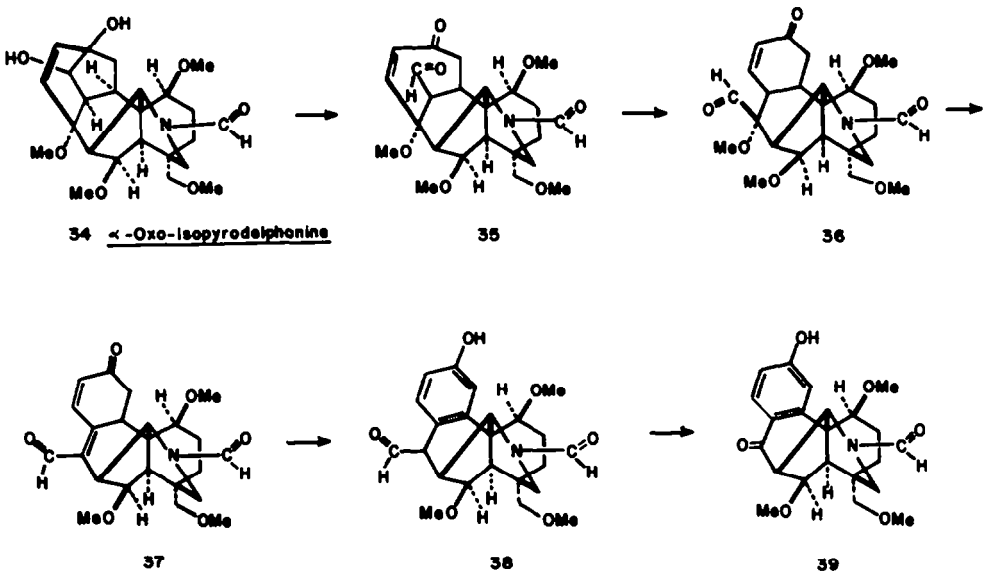
The skeletal structures of all these aconitum alkaloids are simply derivable from the skeleton of atisine and they had an important precedent. Maria Przybylska (National Research Council, Ottawa) determined by X-ray crystallography the structure of lycoctonine (**32**) prior to the completion of our work on delphinine and it was based on the same skeleton. However, the NRC workers did not recognize the striking similarity of the atisine and lycoctonine skeleta and it remained for us and Professor Cookson in England to point out the simple biogenetic relationship of the two structures shown in Scheme 6.[8] While the order of the steps indicated in formula **30** cannot be specified, we found some years later the alkaloid denudatine (**33**) to be a kind of arrested intermediate of the process[9] and we corroborated the denudatine structure by total synthesis.[10]

Finally, I would like to discuss a remarkable degradation of aconitine and delphinine[6,11] which allowed us not only to correlate these two alkaloids,[12] but also to corroborate synthetically both structures.[13] For the sake of brevity, I shall discuss this sequence only for delphinine.

α-Oxoisopyrodelphonine (**34**) was treated with 1 mol of metaperiodate and the resulting seco keto aldehyde (**35**) was stirred with oxygen and alkali. After a few hours, a good yield of the phenol (**39**), which revealed its nature by a typical *p*-hydroxyacetophenone UV spectrum, was isolated from the mixture. The presumed intermediates of this remarkable transformation are given in Scheme 7. We see that all the changes are standard base-catalyzed reactions which require no comment. The last step is an autoxidation which we verified on a model.[11] The aromatization product **39** was characterized as a crystalline methyl ether and its structure was verified by synthesis.[13] Before briefly outlining the strategy of this synthesis, I wish to point out that the aromatization product contains *intact* the entire part of the molecule which was *conjectured*. The part structure transformed to the aromatic nucleus was *rigorously known. Thus delphinine is one of the few very complex compounds for which a rigorous chemical structure proof is available.*

The starting material for the synthesis was the disubstituted tetralone **40** (Scheme 8) which was oxidized to the corresponding keto aldehyde **41**. Base-catalyzed aldolization of this last compound

† I proposed the delphinine structure **27** as one of four possibilities at the Gordon Conference, New Hampton, July 30, 1958.

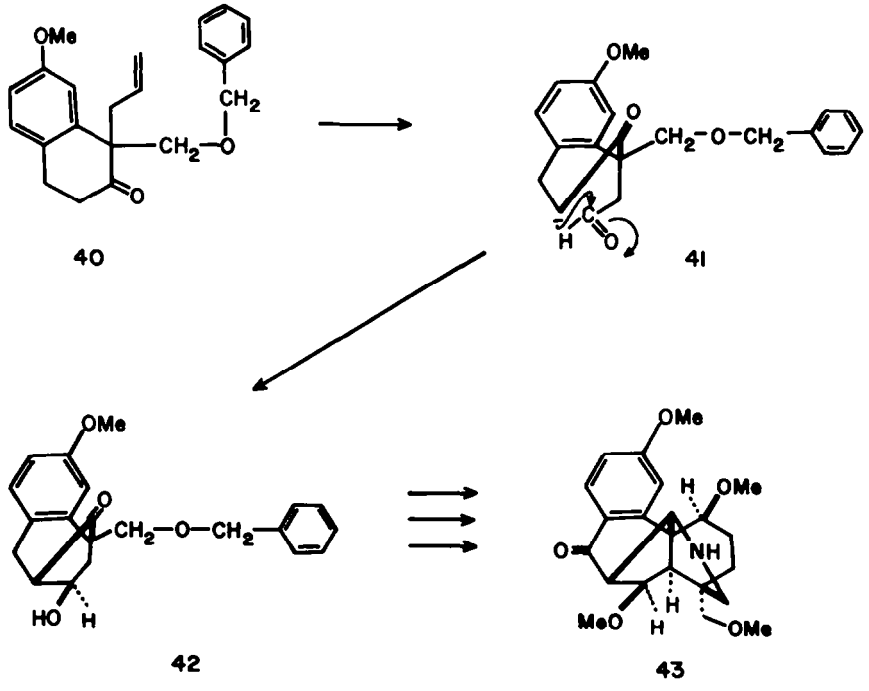


Scheme 7.

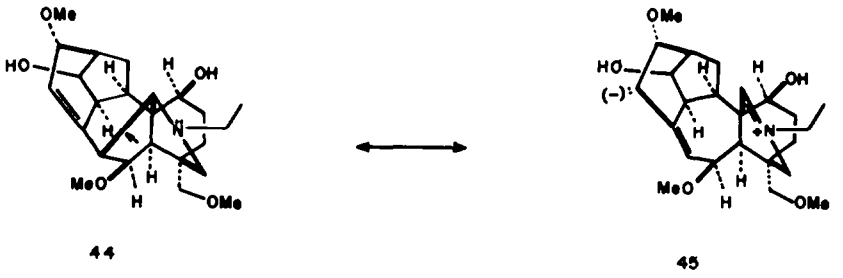
gave the tricyclic synthon **42** in high yield. The disposition of functional groups in **42** is very well suited and it permitted a relatively easy elaboration of this intermediate into the desired product **43**. Finally, a differential reaction of the racemate **43** with *l*-camphorsulphonyl chloride resulted in a very efficient resolution and completed the synthesis of the optically active material.

THE UNPRECEDENTED SPECTRUM OF PYRONEOLINE

One cannot do this kind of work for 30 years without running into something highly unusual which quite unexpectedly leads to a fundamental discovery. When we were working on the structure of neoline we noticed that pyroneoline (**44**) displayed a very unusual UV spectrum (λ_{max}^{EtOH} = 236 nm, log ε

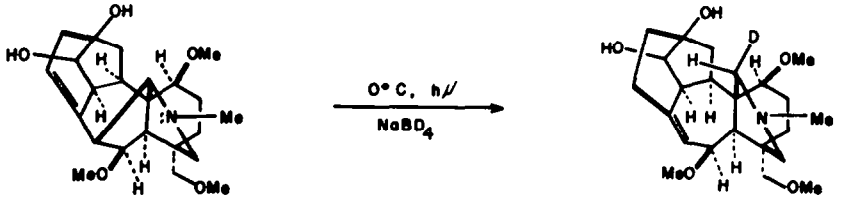


Scheme 8.



44 45

U.V. λ_{max} = 236 nm (log ϵ = 3.85)



46 47

Scheme 9.

= 3.85). In our paper on the structure of neoline[7] we suggested that the π electrons of the double bond, the σ electrons of the ring B bridge (marked by an arrow) and the electron pair of the nitrogen form a chromophore and that the excited state of pyroneoline should be represented as a mesomeric hybrid of the canonical formulae **44** and **45**. Later, Professor Cookson found several similar examples and termed chromophores of this kind "σ coupled π systems".

It was possible to demonstrate the functioning of this novel chromophoric system in the following way. We first removed the allylic methoxyl of pyrodelphonine by a sequence of steps which is unimportant in this connection.† As expected, the resulting desmethoxypyrodelphonine (**46**) still displayed the same unusual UV spectrum of its σ coupled π system.

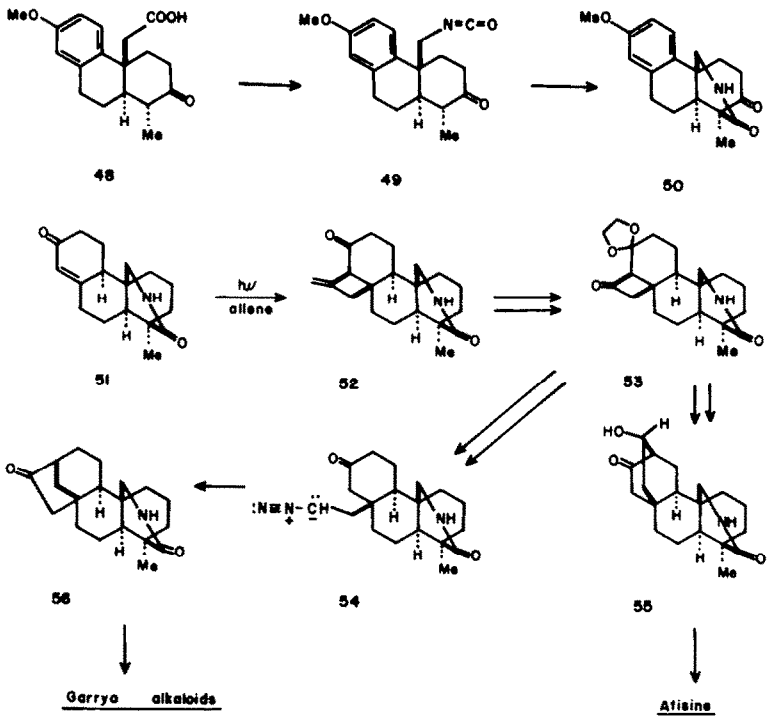
When **46** was exposed to an excess of sodium borohydride in methanol, it turned out to be completely stable. However, irradiation of the mixture led to a smooth photoreduction. When sodium borodeuteride in methanol was used, the monodeuterated photoreduction product **47** was obtained. This result can be readily understood in terms of the reduction of an immonium canonical formula analogous to **45**.

TOTAL SYNTHESIS OF THE SIMPLE C_{20} DITERPENE ALKALOIDS

At this point in time not only all of our structural problems (lycopodium alkaloids, ryanodine and a few others) were solved, but chemical structure determination itself was coming to an end. I decided to turn to synthesis and to develop synthetic methods for some of the compounds that represented milestones of my road in structural chemistry.

We naturally decided to tackle the simple pentacyclic diterpene alkaloids first. The steroid-like backbone of these compounds could be readily constructed if one utilized the know-how accumulated in the total synthesis of steroids. It then remained only to construct the nitrogen bridge and the special features of the diterpene alkaloids. We carried out several syntheses of the Garrya alkaloids and atisine[15] simultaneously and slightly later than the well-known synthetic work of Professors Masamune and Nagata, who, however, used entirely different construction methods.

† The removal of the OMe was necessary since it is well known that this allylic methoxyl readily undergoes a hydride reduction with a simultaneous allylic shift of the double bond.



Scheme 10.

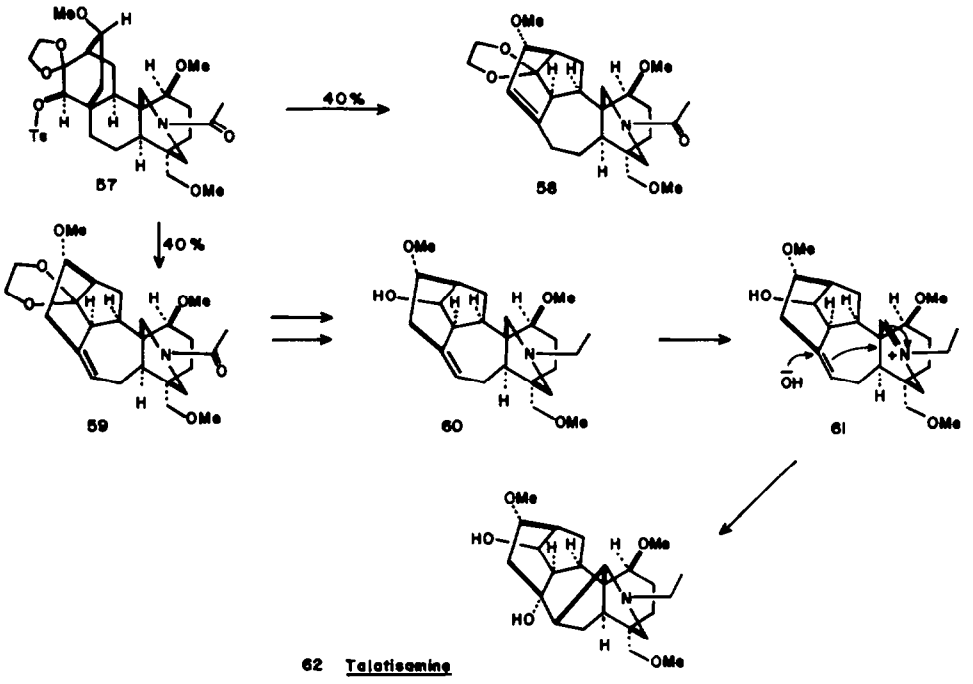
As shown in Scheme 10, the starting material for one of our approaches was the keto acid **48** constructed essentially by methods developed by Sir Robert Robinson and Gilbert Stork. This was simply degraded to the isocyanate **49** which underwent an almost regiospecific acid-catalyzed cyclization to the keto lactam **50**. Only a very small amount of the isomeric compound was formed. Conversion of **50** to the α,β-unsaturated ketone **51** by removal of the keto group and Birch reduction was simple. Photoaddition of allene to **51** gave surprisingly the photoadduct **52** in high yield with complete stereospecificity. This finding was the origin of our photoaddition rule.[16] This rule, in its most empirical form, states that *cis* photoaddition and dissolving metal reduction performed on an α,β-unsaturated ketone will yield major products with the same configuration at the β carbon. The empirical rule has now been abundantly verified and steric hindrance has been ruled out as a major factor controlling the configuration. Work on the theoretical implications of the rule is still in progress.

The photoadduct **52** was simply converted to the cyclobutanone acetal **53**. Borohydride reduction to the corresponding cyclobutanol followed by aqueous acid treatment yielded the bicyclo[2.2.2]octane derivative **55** via a retroaldol–aldol condensation reaction. Compound **55** was elaborated to atisine. Alternatively, the cyclobutanone **53** was opened to a keto acid and converted to the Garrya type skeleton **56** via the diazo intermediate **54**. The keto lactam **56** was resolved into enantiomers and converted to the Garrya alkaloids.

TOTAL SYNTHESIS OF THE HEXACYCLIC POLYSUBSTITUTED DITERPENE ALKALOIDS

The synthesis of atisine and our already mentioned biogenetic hypothesis[8] were the starting point of the first synthesis of a delphinine-type alkaloid, talatisamine.[17] We constructed the intermediate **57** using generally similar methods to those in the synthesis of atisine. Heating of this material with dimethyl sulfoxide and tetramethylguanidine gave the rearrangement products **58** and **59** each in 40% yield. Compound **59** was readily converted to the tertiary amine **60**, which was oxidized by mercuric acetate to talatisamine **62** in a yield of 40%. The oxidation presumably proceeded via the quaternary Schiff salt **61** which cyclized spontaneously to **62**. Precedent for this cyclization was some work of Professor Büchi described in our joint communication.[6]

After all our investment in the diterpene alkaloid field, we were happy to have accomplished this synthesis. At the same time it was clear that as a synthesis it was not good. (1) The introduction of



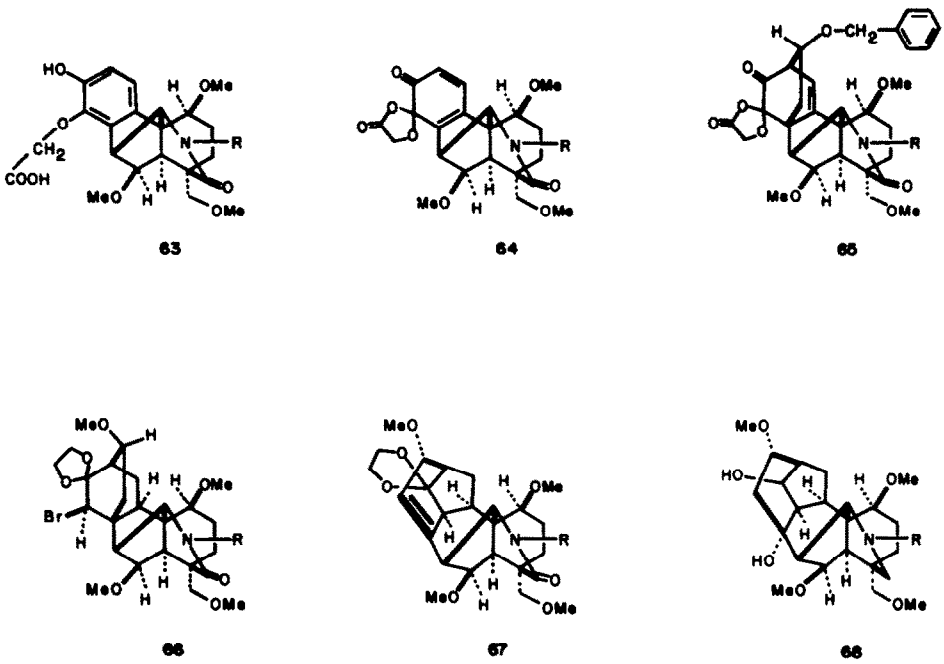
Scheme 11.

substituents in **57** was laborious and could not be improved. (2) Half of the material gave the useless isomer **58**. (3) The mercuric acetate generation of **61** was predictably also unselective and gave another unacceptable 40% yield. (4) Talatisamine was a specially easy target since a crucial substituent was missing.

Careful consideration of the problem made it clear that there was one single remedy which could overcome all these troubles in one stroke. This remedy was to introduce the ring B bridge at the very beginning rather than at the end of the synthesis. As a result of this conclusion, we designed two synthetic schemes which actually used the same strategy and differed only in the chemical implementation. The first one was completed in 1977 and achieved the first synthesis of the fully substituted alkaloid chasmanine.[18] The second one accomplished the same objective in a sequence about 10 steps shorter and an order of magnitude more efficient a year later.[19] Since both these syntheses represent variations on the same theme, I shall discuss briefly only the second one.

The strategy is clearly illustrated in Scheme 12. It started with the stereo- and regiospecific construction of the ring B bridged aromatic intermediate **63**. This material was converted to the masked quinone **64** by the Deslongchamps oxidation with N-bromosuccinimide and a stereospecific *exo*-addition of benzyl vinyl ether yielded the "nordenudatine" intermediate **65**. The functional group system of **65** was first simply and stereospecifically adjusted and the intermediate **66** was subjected to a Wagner rearrangement which yielded the "pyro-oxo" derivative **67**. A further simple adjustment of functionality finally gave the aconite alkaloid **68**.

The strategy which we gradually evolved for the synthesis of the aromatic intermediate **63** is illustrated in Scheme 13. The ester **69** was prepared from *o*-cresol. Diels–Alder addition of maleic anhydride to the *o*-quinonoid tautomer **70** gave a high yield of the adduct (**71**) which was decarboxylated to the olefin **72** by the Trost method (bistriphenylphosphinenickel dicarbonyl). Now came the crucial step which resulted in the high yield stereospecific preparation of the synthon **74**. The *exo*-N-acetylaziridine **73** was formed by treatment of **72** with trimethylsilyl azide followed by acetic acid and acetic anhydride; it rearranged *in situ* stereo- and regiospecifically to **74**. For the success of this rearrangement it was necessary to have a group which was not a strong electron releaser in the *o*-position to the aromatic methoxyl. However, it had to be a group which was readily convertible to a phenol needed for the continuation of the synthesis. After trying everything in the book, we surprisingly settled on a methyl group. This group was converted to the required phenol in two high yield steps,

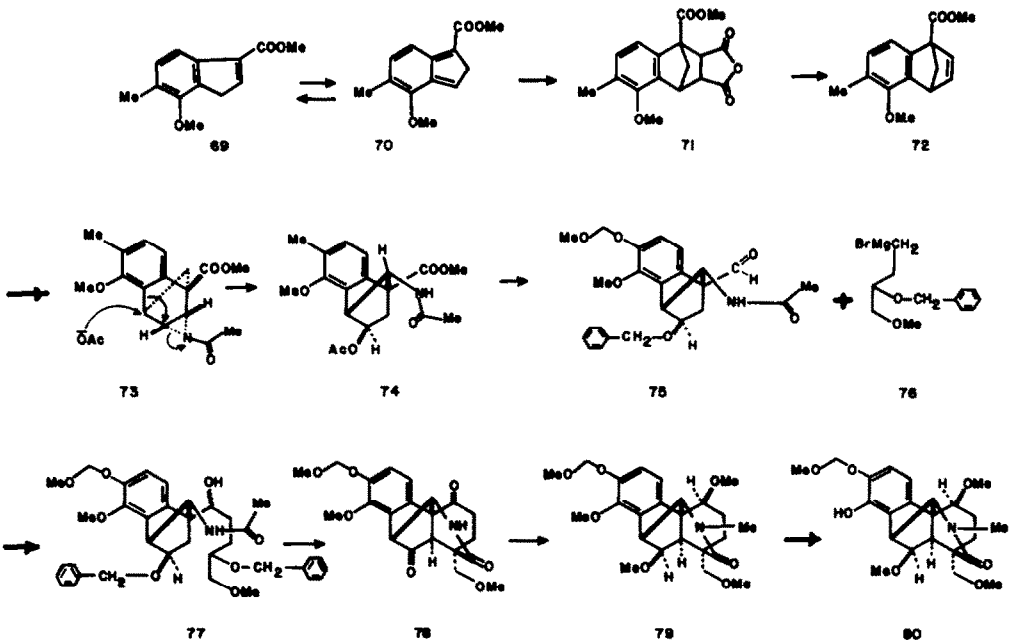


Scheme 12.

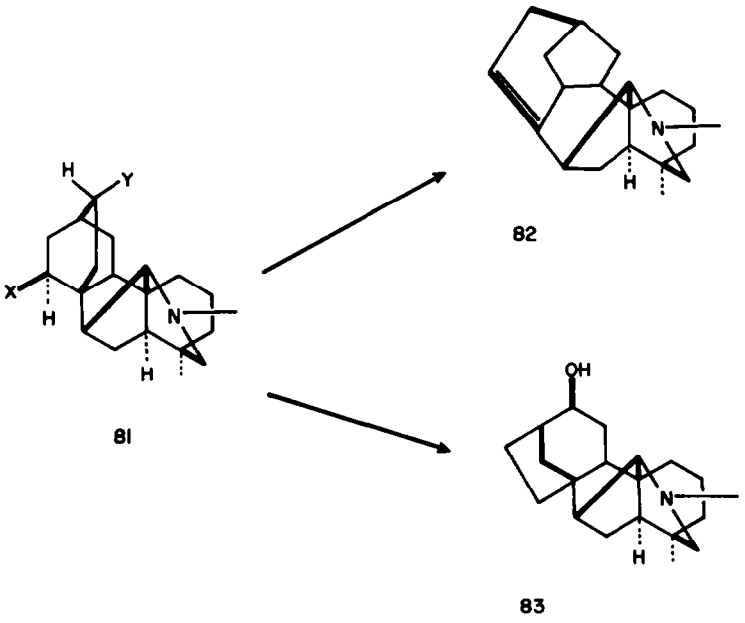
namely by oxidation to an aldehyde with ceric ammonium nitrate followed by a Baeyer–Villiger oxidation.

With the properly modified synthon **75** in hand, its stereospecific conversion to **79** was uneventful. However, one step deserves to be singled out and that is the high yield selective unblocking of the aromatic methoxyl in **79** which was essential to the preparation of **80** and of the aromatic intermediate **63**. This was accomplished by heating with sodium thioethoxide in dimethylformamide.

Thus the final generation of our synthetic studies was completed and our initial objective of



Scheme 13.

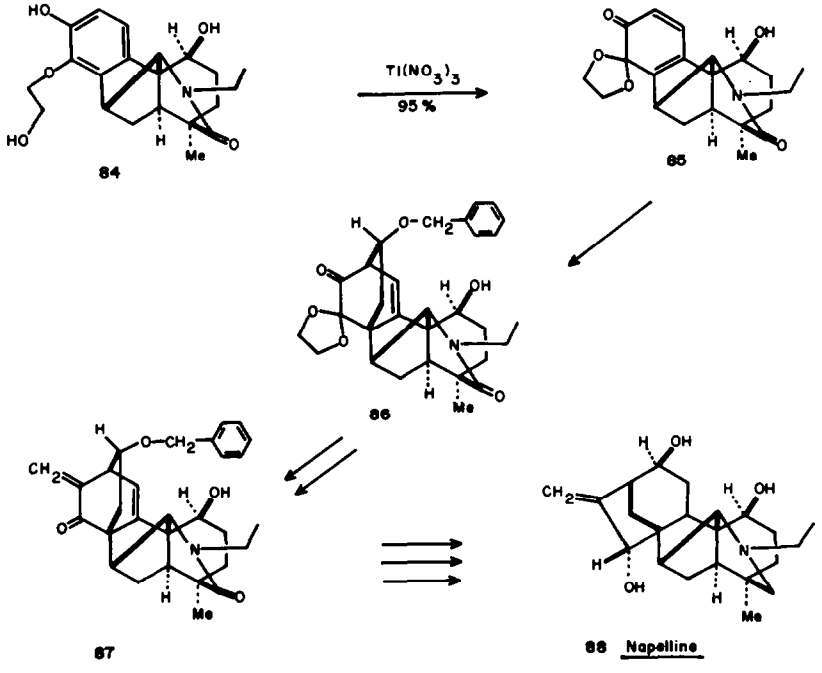


Scheme 14.

simplicity and efficiency was reached to our satisfaction. The entire synthesis proceeded without a relay compound and yielded a good amount of the final crystalline racemic aconite alkaloid.

In conclusion, I would like to touch briefly on our second synthesis[4b] of the alkaloid napelline which played such an important role in the structural studies. Both the delphinine system and the napelline system may be built by basically the same strategy which is illustrated by the formulae **81**, **82** and **83** (Scheme 14).

Ejection of the leaving group X from the denudatine structure **81** followed by rearrangement and deprotonation yields the "pyrodelphinine"-type intermediate **82**. Alternatively, the napelline derivative **83** may be obtained by ejection of the leaving group Y, followed by rearrangement and



Scheme 15.

capture of a nucleophile. This general strategy for napelline was now very simply implemented as follows. The aromatic intermediate **84** (Scheme 15) was synthesized by a routine application of our aziridine rearrangement methodology. Oxidation of **84** with $Tl(NO_3)_3$ yielded 95% of the crystalline and quite stable quinone acetal **85**. Addition of benzyl vinyl ether to **85** yielded the "nordenudatine" derivative **86** in 94% yield with complete stereospecificity.

The last "denudatine" carbon was added to **86** by reaction with trimethylsilylmethylmagnesium chloride followed by acid treatment and the synthesis of the desired denudatine system **87** with a potential leaving group blocked by benzyl was complete. A few trivial functional group manipulations including the already mentioned rearrangement yielded finally the alkaloid napelline **88**. Thus in 1980 the work which started with structural studies on the Garrya alkaloids in 1949 was complete.

Finally, I wish to thank my many younger colleagues for their dedication and inspired hard work. Their names can be found in the references quoted. I wish to point out that this article is not a general review of diterpene alkaloid chemistry. Only key references to the highlights discussed in the article are given. References to both the work of other laboratories and to our own work may be found in these key references.

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